Remarks

Claims 14-36 are pending in the subject application. By this Amendment, Applicant has added new claims 37 and 38. Support for the new claims can be found throughout the subject specification (see, for example, page 6, lines 31-33 and page 7, lines 26-31). Entry and consideration of the new claims presented herein is respectfully requested. Accordingly, claims 14-38 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicant gratefully acknowledges the Examiner's withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 14-36 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that even though Applicant claims a method for treatment of SARS-CoV infection in an individual that includes specific amounts, specific routes of administration, *etc.*, there is no indication from the available literature that *in vitro* and non-human models predict success for such methods in humans. The Office Action also argues that "[a]lthough IFN treatment of SARS-CoV in human (sic) appears to be a reasonable option, especially with IFN-β, the literature is silent regarding the efficacy of such treatment". Applicant respectfully asserts that the claims are enabled by the subject specification and traverse the rejection.

A therapeutic method need not be ready for clinical application in order to be enabled nor is clinical efficacy a requirement for patentability. As stated in *In re Brana*, 51 F.3d 1560, 1567, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.[FN2]." Thus, evidence that a claimed method was not ready for clinical application is not enough to show nonenablement. What is needed is evidence or sound scientific reasoning that undue experimentation would have been required to carry out the claimed methods. While the claims are directed to methods of "treating Severe Acute Respiratory Syndrome (SARS) comprising the administration of a composition comprising an interferon (IFN) to an individual having SARS" and imply some degree of therapeutically beneficial effect, it is clear from the controlling law that the standard for enablement with respect to such methods is more lenient than the standards by which clinical trials are judged. *See, e.g., Brana*, 51 F.3d at 1568, 34 U.S.P.Q.2d at

1442 ("On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical trials .... Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug ... as well as its potential efficacy under different dosage regimens."). Turning to the Examiner's arguments regarding clinical efficacy of the claimed treatment regimen in view of the cited studies used to argue that the literature is silent with respect to the efficacy of treatment protocols such as those claimed herein, Applicant would respectfully submit that efficacy is not required to enable the claims. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 U.S.P.Q.2d 1940, 1944 (Fed. Cir. 2003) ("Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace."); *In re Brana*, 51 F.3d at 1569, ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.").

Applicant also notes that Hensley *et al.* (*Emerging Infectious Diseases*, 2004, 10:317-319, copy attached) reports the results of Interferon-β 1A on SARS-CoV replication. In this report, IFN-β 1A is reported to decrease the SARS-CoV replication and pretreatment or postinfection treatment of Vero E-6 cells with IFN-β 1A provided "dramatic" protection against the cytopathic effects caused by SARS-CoV (see page 317, column 2, first full paragraph). While pretreatment of the cells resulted in ≥ 99.5% reduction in the production of infectious SARS-CoV, post infection treatment of cells with IFN-β 1A resulted in a ≥ 90% reduction in the production of infectious SARS-CoV. Applicant further notes that the paragraph bridging pages 317-318 of the reference indicates that the "report suggests that IFN-β 1A may be effective as a treatment for SARS-CoV infections" and that "IFN-β 1A exhibited potent antiviral activity at doses that have already been shown to have acceptable safety profiles in animals (10). Thus, we report the identification of a compound that may be suitable for rapid development as a treatment of SARS-CoV infection." Thus, Applicant respectfully submits that the as-filed specification would have enabled one skilled in the art to practice the claimed invention without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

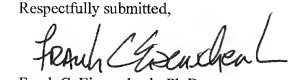
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position. Applicant expressly reserves the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Interferon-β 1a and SARS Coronavirus Replication

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A global outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus began in March 2003. The rapid emergence of SARS and the substantial illness and death it caused have made it a critical public health issue. Because no effective treatments are available, an intensive effort is under way to identify and test promising antiviral drugs. Here, we report that recombinant human interferon -β 1a potently inhibits SARS coronavirus replication in vitro.

The recent global outbreak of severe acute respiratory syndrome (SARS) has quickly gained notoriety as a newly emerging infectious disease. The etiologic agent was identified as a coronavirus (SARS-CoV) that is not closely related to any of the previously characterized coronaviruses (1,2). As of September 26, 2003, a total of 8,098 probable cases of SARS have occurred with 774 deaths.

No antiviral treatments are currently available against SARS-CoV. SARS cases have been treated symptomatically according to the severity of the illness. A treatment protocol consisting of antibacterial agents and a combination of ribavirin and methylprednisolone was recently proposed. However, the therapeutic value of ribavirin remains uncertain because it has no activity against SARS-CoV in vitro. Molecular modeling studies suggest that rhinovirus $3C^{pro}$ inhibitors may be useful for SARS therapy, but results of recent in vitro testing of the lead molecule, AG7088, were negative (3).

Previous studies showed that some coronaviruses, including avian infectious bronchitis virus, murine hepatitis virus, and human coronavirus 229E, are susceptible to type I interferons in vitro or in vivo (4–7). Therefore, we evaluated the in vitro efficacy of a recombinant human type I interferon (IFN), IFN-β 1a (Serono International, Geneva, Switzerland) against three different isolates of SARS-CoV (Tor2 and Tor7 and Urbani) using yield reduction assays. The IFN-β 1a preparation employed in this study was selected because it is currently used as part of the most effective treatment regimen for relapsing forms of multiple sclerosis (8), and more importantly, because it was shown to have antiviral activity (as measured in a vesicular stomatitis virus cytopathic assay system) 14 times greater than the currently available treatment using IFN-β 1b (9).

In the current study, Vero E6 cells were treated with concentrations (5,000 to 500,000 IU/mL) of IFN-β 1a either 24 h before or 1 h after inoculation with the SARS-CoV (multiplicity of infection 0.1 PFU/cell), and monitored for cytopathic effect and production of infectious SARS-CoV at 24, 48, and 72 h postinfection. Inhibition of the SARS-CoVs by IFN-β 1a was dependent on both time of drug administration and time of culture sampling after SARS-CoV infection. Production of infectious SARS-CoV was potently inhibited (≥99.5% or 2.00 $\log_{10}$ PFU/mL) at 24 h postinfection by pretreatment of Vero E6 cells with IFN-β 1a at all concentrations tested (Figure 1). By 72 h postinfection, inhibition of SARS-CoV production by IFN-β 1a had declined for all three SARS-CoVs, with inhibition (≥70%) being detected in the Tor7 (Figure 1) and Urbani isolates (data not shown). IFN-β 1a was somewhat less effective at inhibiting SARS-CoV replication when employed after infection of cultures (Figure 1). Nonetheless, production of infectious SARS-CoVs was considerably reduced (≥90% or 1.00 $\log_{10}$ PFU/mL) at 24 and 48 h postinfection. Protection of Vero E6 monolayers against SARS-CoV induced cytopathic effects by preinfection or postinfection treatment with IFN-β 1a was dramatic, even at 72 h postinfection (Figure 2). Additional concentrations of IFN-β 1a (0.5–5,000 IU/mL) were tested to determine the 50% inhibitory concentration (IC_{50}). Pretreatment of Vero E-6 cells with concentrations as low as 50 IU/mL, or posttreatment of cells with concentrations at 500 IU/mL, provided a 50% reduction with the Tor2 isolate at 24 h postinfection.

Faced with a burgeoning epidemic of SARS cases and a lack of effective treatment options, identifying compounds with antiviral activity that could be potential therapeutics has become a high priority. Our report suggests

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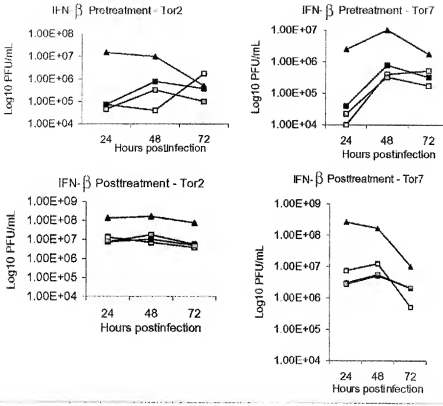

Figure 1. Interferon (IFN)-β 1a inhibition of SARS-CoV replication in Vero E6 cells. Top panels, Vero E6 cells were incubated in the absence (-▲-) or presence of IFN-β 1a added 24 h before infection with the Tor2 (left) or Tor7 (right) isolate of SARS Co-V. Bottom panels, Vero E6 cells were incubated in the absence (-▲-) or presence of IFN-β 1a added 1 h after infection with the Tor2 (left) or Tor7 (right) isolate of SARS Co-V. Three concentrations of IFN-β 1a were employed for both studies: 5,000 IU/mL (-□-), 50,000 IU/mL (-●-), 500,000 IU/mL (-■-) Samples of overlying media were collected at 24, 48, and 72 h postinfection and analyzed by plaque assay on Vero E6 cells.

that IFN-β 1a may be effective as a treatment for SARS-CoV infections. As noted above, IFN-β 1a is currently being used for a variety of clinical indications, including multiple sclerosis, and has shown dose-dependent efficacy in several clinical trials. Importantly, IFN-β 1a exhibited potent antiviral activity at doses that have already been shown to have acceptable safety profiles in animals (10). Thus, we report the identification of a compound that may be suitable for rapid development as a treatment for SARS-CoV infection.

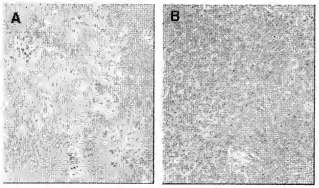

Figure 2. Interferon (IFN)-β 1a inhibition of SARS-CoV cytopathicity in Vero E6 cells. Vero E6 cells were infected with the Tor2 isolate of SARS-CoV and incubated for 72 h in the absence (left panel) or presence (right panel) of 500,000 IU of recombinant human IFN-β 1a. Cell rounding and detachment were prominent in the absence of IFN-β 1a. Minimal cell rounding or death was noted in the intact monolayer at 72 h postinoculation in the presence of IFN-β 1a (note: IFN-β 1a administered 1 h postinfection).

Acknowledgments

We thank Dr. Heinz Feldman for his kind provision of Tor2 and Tor7 isolates.

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